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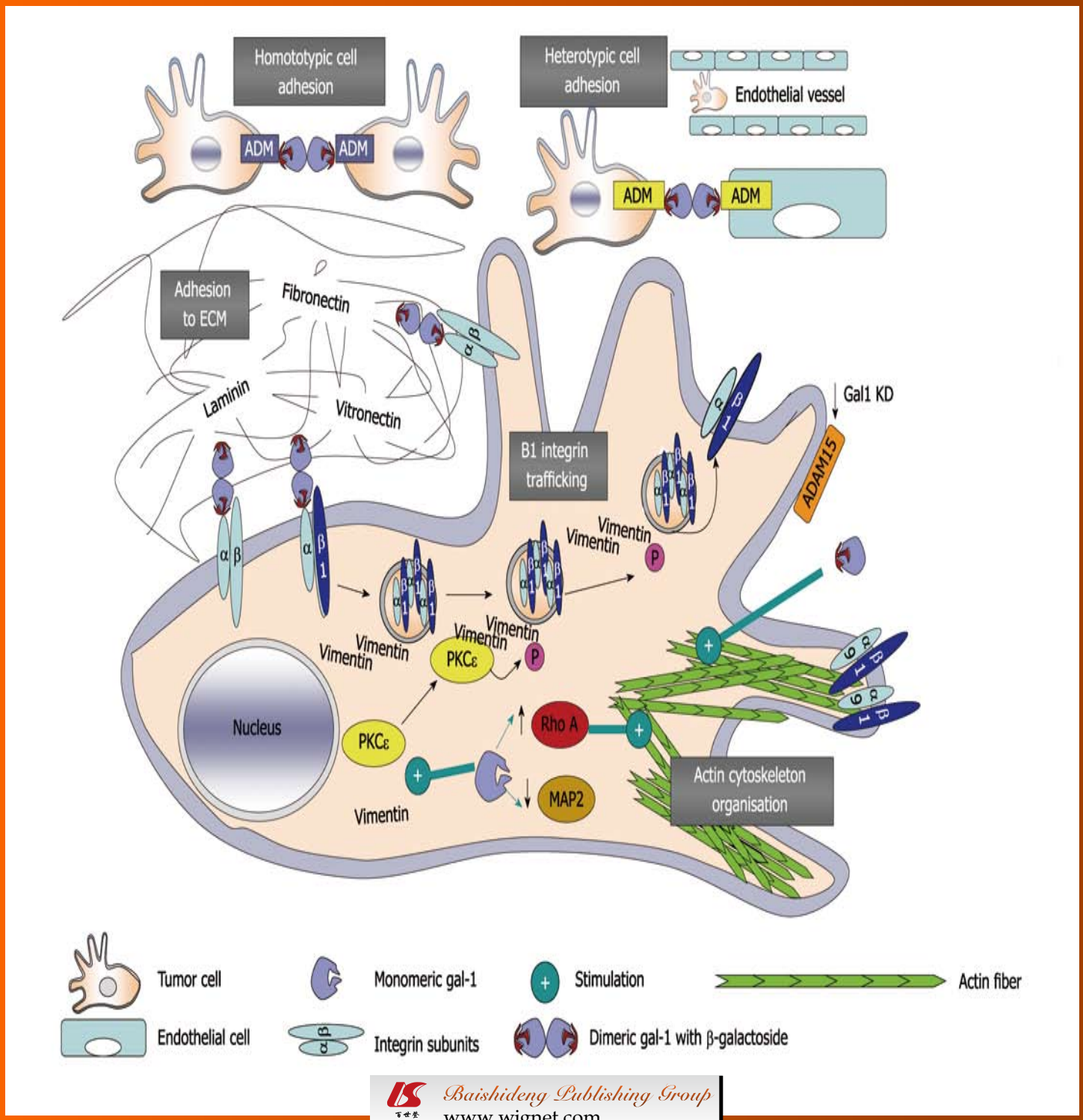

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No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
E-mail: wjbc@wjgnet.com
http://www.wjgnet.com

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EDITORIAL

Galectin-1-mediated biochemical controls of melanoma and glioma aggressive behavior

Florence Lefranc, Véronique Mathieu, Robert Kiss

Florence Lefranc, Véronique Mathieu, Robert Kiss, Laboratory of Toxicology, Faculty of Pharmacy, Université Libre de Bruxelles, Brussels 1050, Belgium
Florence Lefranc, Department of Neurosurgery, Erasme Academic Hospital, Brussels 1050, Belgium
Author contributions: Lefranc F and Kiss R wrote the article; Mathieu V wrote part of the article and drew the figures.
Supported by Fonds National de la Recherche Scientifique (FNRS; Belgium)
Correspondence to: Robert Kiss, Professor, PhD, Laboratory of Toxicology, Faculty of Pharmacy, Université Libre de Bruxelles, Campus de la Plaine, Boulevard du Triomphe, Brussels 1050, Belgium. rkiss@ulb.ac.be
Telephone: +32-477-622083 Fax: +32-2-3325335
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Abstract

Gliomas and melanomas are associated with dismal prognosis because of their marked intrinsic resistance to proapoptotic stimuli, such as conventional chemotherapy and radiotherapy, as well as their ability to escape immune cell attacks. In addition, gliomas and melanomas display pronounced neoangiogenesis. Galectin-1 is a hypoxia-sensitive protein, which is abundantly secreted by glioma and melanoma cells, which displays marked proangiogenic effects. It also provides immune tolerogenic environments to melanoma and glioma cells through the killing of activated T cells that attack these tumor cells. Galectin-1 protects glioma and melanoma cells against cytotoxic insults (including chemotherapy and radiotherapy) through a direct role in the unfolded protein response. Altogether, these facts clearly point to galectin-1 as an important target to be combated in gliomas and melanomas in order to: (1) weaken the defenses of these two types of cancers against radiotherapy, chemotherapy and immunotherapy/vaccine therapy; and (2) reinforce antiangiogenic therapies. In the present article, we review the biochemical and molecular biology-related pathways controlled by galectin-1, which are actually beneficial for melanoma and glioma cells, and therefore detrimental for melanoma and glioma patients.

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Key words: Galectin-1; Glioma; Melanoma; Biochemical pathways

Peer reviewers: Ming Zhang, PhD, Associate Professor, Department of Molecular Pharmacology and Biological Chemistry, Feinberg School of Medicine Northwestern University, 303 E. Superior St., Chicago, IL 60611, United States; Shile Huang, PhD, Associate Professor, Department of Biochemistry and Molecular Biology, Louisiana State University Health Sciences Center, Shreveport, LA 71130-3932, United States; Tatjana Abaffy, Dr, Molecular and Cellular Pharmacology, University of Miami, Miller School of Medicine, 1600 NW 10 Ave, Miami, FL 33136, United States

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AN OVERVIEW OF THE BIOLOGICAL ROLES OF GALECTIN-1

Galectin-1 is a 14.5-kDa β-galactoside-binding protein that belongs to a 15-member protein family[1-4], which are all evolutionarily well conserved[5], expressed by many different cell types[1-4] with major roles exerted in the immune system[6-9] and involved in the progression of various cancer types[2,3,10], including melanomas[7,11-14] and gliomas[15-20].

Galectin-1 belongs to the prototype galectins, which are characterized by one carbohydrate recognition domain (CRD) that can occur as a monomer or as a non-covalent homodimer consisting of subunits of a single CRD (galectin-1, about 29 kDa)[1-4]. Galectin-1 is functionally present intracellularly (cytosol, nuclei and intracellular plasma membrane) and extracellularly (extracellular cell membrane and extracellular matrix)[4]. Although galectins as a whole do not have the signal sequence required for protein secretion, galectin-1 is secreted by a yet unidentified export mechanism that bypasses the classical endoplasmic reticulum/Golgi apparatus-dependent secretory pathway that appears to balance tightly between intra- and extracellular galectin-1[21,22].

In addition to its carbohydrate-binding ability, galectin-1 is able to perform protein–protein interactions[23,24]. As a result, it participates in a variety of oncogenic processes including cell transformation[2,3,4,10], cell proliferation *vs* cell death[25-28], cell migration[2,3,4,18,29-31], metastasis[2,3,4,10] and angiogenesis[32-35]. As detailed below, galectin-1 also exerts subtle biochemical controls including modulations of the unfolded protein response (UPR)[33,36], following cytotoxic insults contributed by chemotherapy[11,36] and radiotherapy[37], as well as potential roles in mRNA splicing[38-40].

All these biological roles played by galectin-1 occur through the interactions with a myriad of extracellular and intracellular ligands and/or receptors including, but not limited to, laminin, fibronectin, vitronectin, integrins, CA-125, H-ras, CD45 and gemin-4[1-4,18,19]. Galectin-1 also plays major roles in tumor immune escape processes and in tuning the immune response. This aspect of galectin-1-related functions has been extensively reviewed[8,41-43] and is not further discussed here. Figure 1 illustrates the overall picture of galectin-1-related major roles in tumor cell biology.

GALECTIN-1 AND MELANOMAS

Although melanomas account for only 4% of all dermatological cancers, they are responsible for 80% of deaths from skin cancer[44,45]. In fact, the incidence of melanoma is increasing worldwide, and the prognosis for patients with high-risk or advanced metastatic melanoma remains poor despite advances in the field[44]. Patients who progress to stage Ⅳ metastatic melanoma have a median survival of < 1 year[44]. Only 14% of patients with metastatic melanoma survive for 5 years[46]. Melanomas display both intrinsic and acquired resistance to proapoptotic stimuli[47], while most chemotherapeutic agents still used to combat melanoma are proapoptotic agents[48,49].

Great hope has been placed in vaccines, but only limited successes have been observed to date[44]. Indeed, clinical trials of melanoma vaccines have yielded inconclusive data on whether a positive melanoma-specific immune response predicts treatment benefit[45]. In fact, melanoma cells are able to escape natural, endogenous or therapeutically induced immune attacks[50]. The Rabinovich group[7,8] has elegantly demonstrated that melanoma-secreted galectin-1 induces apoptosis of activated T cells through recognition of glycosylated CD3, CD7 and CD45, thereby constituting an important mechanism of tumor escape in experimental melanomas. The blockade of this inhibitory signal can allow for and potentiate effective immune responses against melanoma cells with profound implications for cancer immunotherapy. Decreasing galectin-1 expression in melanoma could be achieved through the use of anti-galectin-1 siRNA, which we have developed[51] and aim to use for vaccine therapy in glioma patients[19] as detailed below.

Melanomas are associated with marked angiogenesis[52], and hypoxia favors melanoma progression[53]. Galectin-1 is a hypoxia-inducible protein[54,55] with marked proangiogenic effects[32-35] that have been demonstrated in experimental melanomas[11]. Great hope has also been placed in antiangiogenic therapies to combat melanomas[56,57], and decreasing galectin-1 expression in melanomas would be one strategy to accomplish this.

The PubMed database already includes about 2800 publications on galectins as of September 2011 with 920 of them related to galectin-1, but only 17 publications cross-reference melanoma and galectin-1, and they often do so indirectly. In other words, little information is available about the exact roles of galectin-1 in melanoma biology. The first report was published in 1995 by van den Brûle *et al*[58], who have shown that galectin-1 modulates human melanoma cell adhesion to laminin. Subsequently, galectin-1 has been demonstrated to participate in the aggregation of human melanoma cells through binding to the 90K/MAC-2BP glycoprotein[59]. As mentioned above, Rabinovich and his group have demonstrated the roles of galectin-1 in immune tumor escape processes using an experimental melanoma model[7]. We have used the same model to demonstrate the protective roles of galectin-1 against chemotherapy-induced cytotoxic insults in melanoma cells[11]. Although Rondepierre *et al*[14] have demonstrated a direct role for galectin-1 in the biological aggressiveness of experimental melanomas, Bolander *et al*[12] have failed to observe any correlation between the levels of galectin-1 expression in melanoma and patient survival. Nevertheless, our recent clinical data have indicated that galectin-1 is particularly highly expressed in advanced melanoma lesions, notably in comparison to galectin-3 and -9 (submitted manuscript).

Altogether, these data that are already available in the literature strongly suggest that galectin-1 could be implicated in various biological processes linked to melanoma progression, such as tumor immune escape, tumor angiogenesis and chemoresistance. However, most of these data are from experimental models, and clinical confirmation of these findings is warranted.

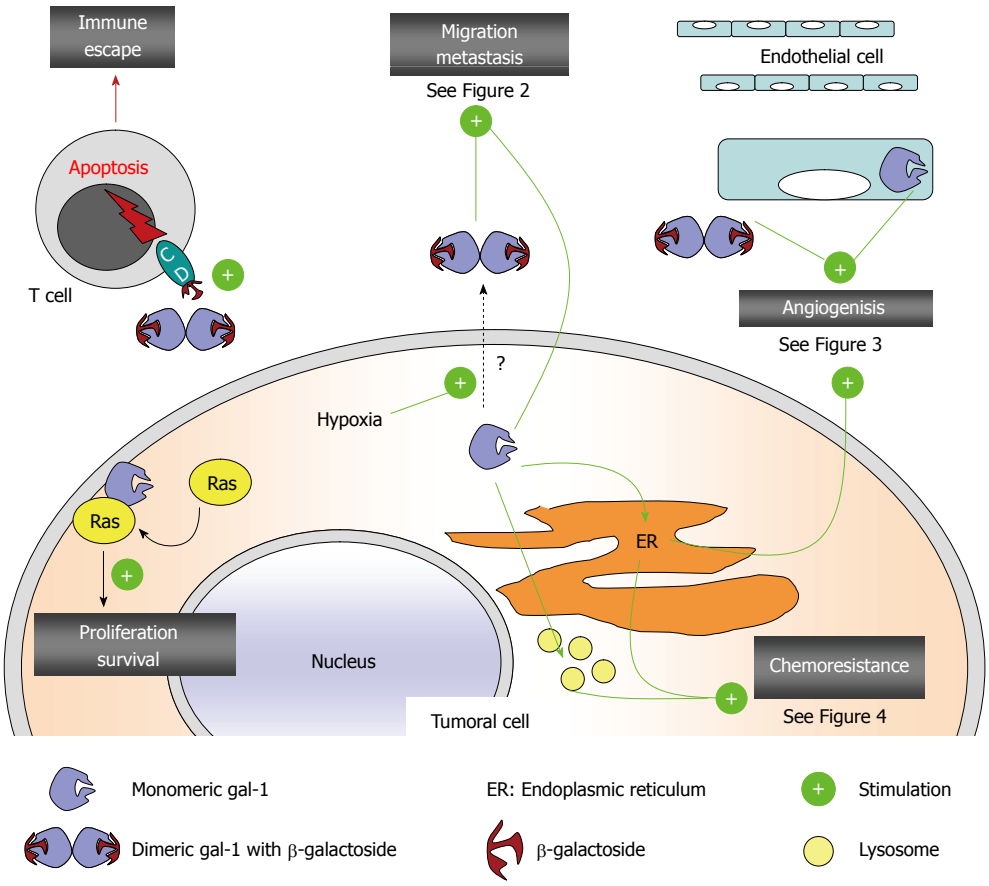

Figure 1 Major roles of galectin-1 in tumor biology. CD: Cluster of differentiation antigen, could be CD2, CD3, CD7, CD29, CD43 and/or CD45 that are expressed at the cell surface of activated T cell and that display typical β-galactosides recognized by galectin-1.

GALECTIN-1 AND GLIOMAS

There are 19 publications available in the PubMed database with cross references about galectin-1 and gliomas and 17 with cross references about galectin-1 and melanomas (as of July 2011). However, much more information is available about how galectin-1 controls glioma cell biology than melanoma cell biology.

Gliomas are the most common primary brain tumors, among which glioblastoma (GBM) is the most malignant form. Malignant gliomas, especially GBMs, are characterized by the diffuse invasion of distant brain tissue by a myriad of single migrating cells with reduced levels of apoptosis and consequent resistance to the cytotoxic insults of proapoptotic drugs[60-62]. In contrast, GBM cells are less resistant to cell death induced by sustained proautophagic processes[62]. Current clinical recommendations for treating malignant glioma patients, and more specifically GBM patients, include maximum surgical resection followed by concurrent radiation and chemotherapy with temozolomide[62-64]. This clinical protocol is now the standard of care for treating GBM patients, and the overall survival rates have increased from 11% to 27% at 2 years, from 4% to 16% at 3 years, from 3% to 12% at 4 years, and from 2% to 10% at 5 years, compared to surgery and radiotherapy alone[63,64].

As detailed below, galectin-1 significantly affects glioma progression. Experimental data have already been validated, at least partly, by clinical data. By using computer-assisted microscopy, we have quantitatively characterized the levels of expression of galectins-1, 3 and 8 in 116 human astrocytic tumors of grades I -IV by immunohistochemistry. The data have indicated that the levels of galectin-1 and 3 expression significantly changes during the progression of malignancy in human astrocytic tumors, whereas galectin-8 remains unchanged[16]. We have extended our analyses to include a quantitative immunohistochemical determination of galectin-1 expression in 220 gliomas, including 151 astrocytic, 38 oligodendroglial and 31 ependymal tumors obtained from surgical resections[65]. We have also xenografted three human glioblastoma cell lines (H4, U87 and U373 models) into the brains of nude mice to characterize the *in vivo* galectin-1 expression pattern following subsequent invasion into the normal brain parenchyma[65]. In addition, we have characterized *in vitro* the role of galectin-1 in U373 tumor astrocyte migration and kinetics. Our data have revealed expression of galectin-1 in all human glioma types, with no striking differences between astrocytic, oligodendroglial and ependymal tumors[65]. The level of galectin-1 expression is correlated only with grade of astrocytic tumors[65]. Furthermore, immunopositivity of high-grade astrocytic tumors from patients with short-term survival periods is stronger than tumors from patients with long-term

survival[65]. In human glioblastoma xenografts, galectin-1 is preferentially expressed in the more invasive parts of the xenografts[65]. *In vitro* experiments have revealed that galectin-1 stimulates the migration of U373 astrocytes[65]. Most of these data that we have produced[16,65] along with Yamaoka *et al*[15], have been validated by Jung *et al*[17].

We recently have reviewed the general roles of galectins, in particular galectin-1, in gliomas[18]. We therefore focus our attention below on the biochemical pathways in which galectin-1 is implicated when controlling various processes related to glioma progression and to a lesser extent, melanoma progression.

As mentioned earlier, we do not review in detail the marked roles exerted by galectin-1 when tuning the immune system response, and those associated with the tumor immune escape phenomenon, because all these aspects have been reviewed in depth by others[8,41-43]. Nevertheless, we highlight galectin-1 as a major target to combat gliomas when vaccine therapy is proposed for gliomas[66] and melanomas. Active specific immunotherapy based on dendritic cell vaccination is indeed considered to be a new promising concept aimed at generating an antitumoral immune response in malignant gliomas and melanomas that still have dismal prognosis despite multimodal treatments[19,66]. However, it is now widely accepted that the success of immunotherapeutic strategies to promote tumor regression will rely not only on enhancing the effector arm of the immune response, but also on the downregulation of the counteracting tolerogenic signals[19,66]. We recently reviewed why galectin-1 should be actively targeted to lower glioma-mediated immune escape during vaccine therapy[19].

GALECTIN-1 CONTROLS GLIOMA CELL MIGRATION

Although cell migration is the net result of adhesion, motility and invasion[60], galectin-1 modifies each of these three cell-migration-related processes in glioma cells.

Immunohistochemical analysis of galectin-1 expression in human U87 and U373 glioblastoma xenografts from the brains of immunodeficient mice has revealed a higher level of galectin-1 expression in invasive areas compared with non-invasive areas of the xenografts[16,65,67]. Immunodeficient mice intracranially grafted with U87 or U373 cells that constitutively express low levels of galectin-1 (by stable transfection of an expression vector containing the antisense mRNA of galectin-1) have longer survival periods than those grafted with U87 or U373 cells that express normal levels of galectin-1,[67], and galectin-1 added to the culture medium markedly increases the motility of human neoplastic astrocytes[16,65,67]. We have demonstrated that these effects are at least partly related to marked modifications in the organization of the actin cytoskeleton and increases in small GTPase RhoA expression[67]. We have also investigated stable knockdown of galectin-1 in human U87 glioblastoma cells, and observed major alterations in gene expression when we used cDNA microarray analysis. Among the 631 genes tested that are potentially involved in cancer, the expression of 86 genes was increased at least twofold[68], including ADAM-15 (disintegrin and metalloproteinase domain-containing protein 15) and microtubule-associated protein (MAP) 2, and expression of these proteins was confirmed by immunocytochemistry[68]. The major differences in the patterns of the actin stress fiber organization have also been observed[68], as previously reported for other glioma models[67], and U87 glioma cells that are stably deficient for galectin-1 expression are significantly less motile than control cells[68], as previously observed[67].

Genes whose patterns of expression markedly change during galectin-1 knockdown include α-7/β-1 and α-9/β-1 integrins[68]. These data must be analyzed in parallel with those we report above with respect to galectin-1-mediated modifications in ADAM-15 expression because the ADAM family of membrane-anchorage glycoproteins encompass a catalytically active matrix metalloproteinase domain and a disintegrin domain, and may also be involved in the proteolytic cleavage of cell-surface proteins and in integrin-mediated cell adhesion (including α-9/β-1 integrin/ADAM-15 interactions) *via* RGD-dependent and -independent binding[68]. Using immunofluorescence approaches, we observed that the depletion of galectin-1 through both stable knockdown and transient-targeted siRNA treatments induced an intracellular accumulation of β-1 integrin, along with a decrease in the expression of this integrin at points of adhesion on the cell membrane[69]. Galectin-1 depletion does not alter the gene expression level of β-1 integrin[69]. Transient galectin-1 depletion induces perinuclear accumulation of protein kinase C (PKC)ε and intermediate filament vimentin, both of which have been shown to mediate integrin recycling in motile cells. These data emphasize the involvement of galectin-1 in the PKCε/vimentin-controlled trafficking of β-1 integrin in glioma cells. Figure 2 illustrates the gross picture of galectin-1-related major roles in glioma cell migration.

GALECTIN-1 CONTROLS NEOANGIOGENESIS IN GLIOMAS AND MELANOMAS

As mentioned earlier, galectin-1 is a hypoxia-regulated protein[54,55] that has been shown to have major roles in angiogenesis[32,35] of gliomas[33] and melanomas[11]. We first highlighted that galectin-1 depleted melanoma tumors *in vivo* display lower angiogenesis levels in close association with marked necrotic processes[11]. We have recently begun to decipher the molecular and biochemical pathways through which galectin-1 controls angiogenesis. In gliomas, we have demonstrated that galectin-1 signals through the IRE-1α (endoplasmic reticulum transmembrane kinase/ribonuclease inositol-requiring 1α), which

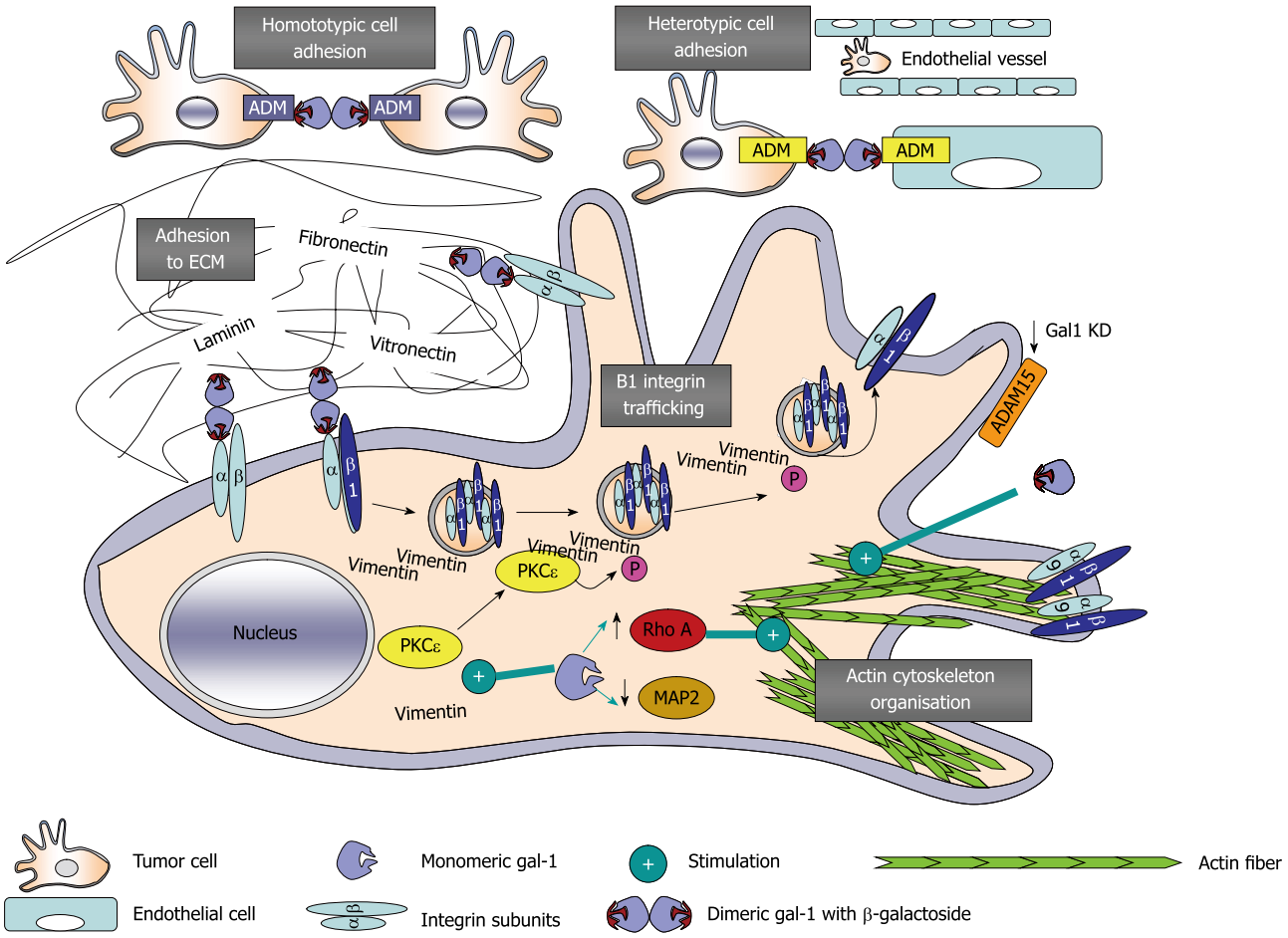

Figure 2 Processes and pathways mediated by galectin-1 in cancer cell migration. ADM: Adhesion molecules; ADAM-15: Disintegrin and metalloproteinase domain-containing protein 15; ECM: Extracellular matrix; MAP2: Microtubule-associated protein 2; P: Phosphorylation; PKCε: Protein kinase C ε; RhoA: Ras homolog protein, member A GTPase.

regulates the expression of oxygen-regulated protein 150 (ORP150) that in turn controls vascular endothelial growth factor (VEGF) maturation[33]. Thus, galectin-1 controls glioma angiogenesis through ORP150-mediated VEGF maturation[33]. Similarly, galectin-1 depletion is associated with decreased ORP150 expression level in melanoma cells (unpublished data). Galectin-1 also modulates the expression of several other hypoxia-related genes (e.g. CTGF, ATF3, PPP1R15A, HSPA5, TRA1 and CYR61) in the Hs683 glioma model, which are known to display various roles in angiogenesis, which we have demonstrated in galectin-1-dependent angiogenesis in glioma[33].

We have observed a marked decrease in the expression of the brain-expressed X-linked gene, BEX2, with decreased galectin-1 expression in glioma cells through targeted anti-galectin-1 siRNA[34]. We have thus focused on BEX2, and observed that decreasing BEX2 expression in human Hs683 glioma cells increased the survival of Hs683 orthotopic xenograft-bearing immunodeficient mice, whose tumors displayed decreased angiogenic levels[34]. Furthermore, this decrease in BEX2 expression impaired vasculogenic mimicry channel formation *in vitro*, as observed when depleting galectin-1 in both glioma and melanoma cells. Thus, BEX2 is a second target, in addition to ORP150, through which galectin-1 controls angiogenesis in gliomas.

BEX2 also modulates glioma cell migration at both adhesion and invasion levels through the modification of several genes previously reported to play a role in cancer cell migration, including MAP2, plexin C1, SWAP70, and β-6 integrin[34].

Galectin-1 controls key angiogenic factors/ pathways in tumoral cells. In addition, galectin-1 has been shown to regulate directly the biological properties of endothelial cells, such as proliferation, activation and *in vitro* tubular network formation[32,35]. We have observed earlier that galectin-3 also participates in glioma angiogenesis[70].

GALECTIN-1 AND ITS MODULATING ROLES IN CHEMOTHERAPY AND RADIOTHERAPY IN THE SPECIFIC CONTEXT OF MELANOMAS AND GLIOMAS

Intratumoral hypoxia causes genetic changes in cancers

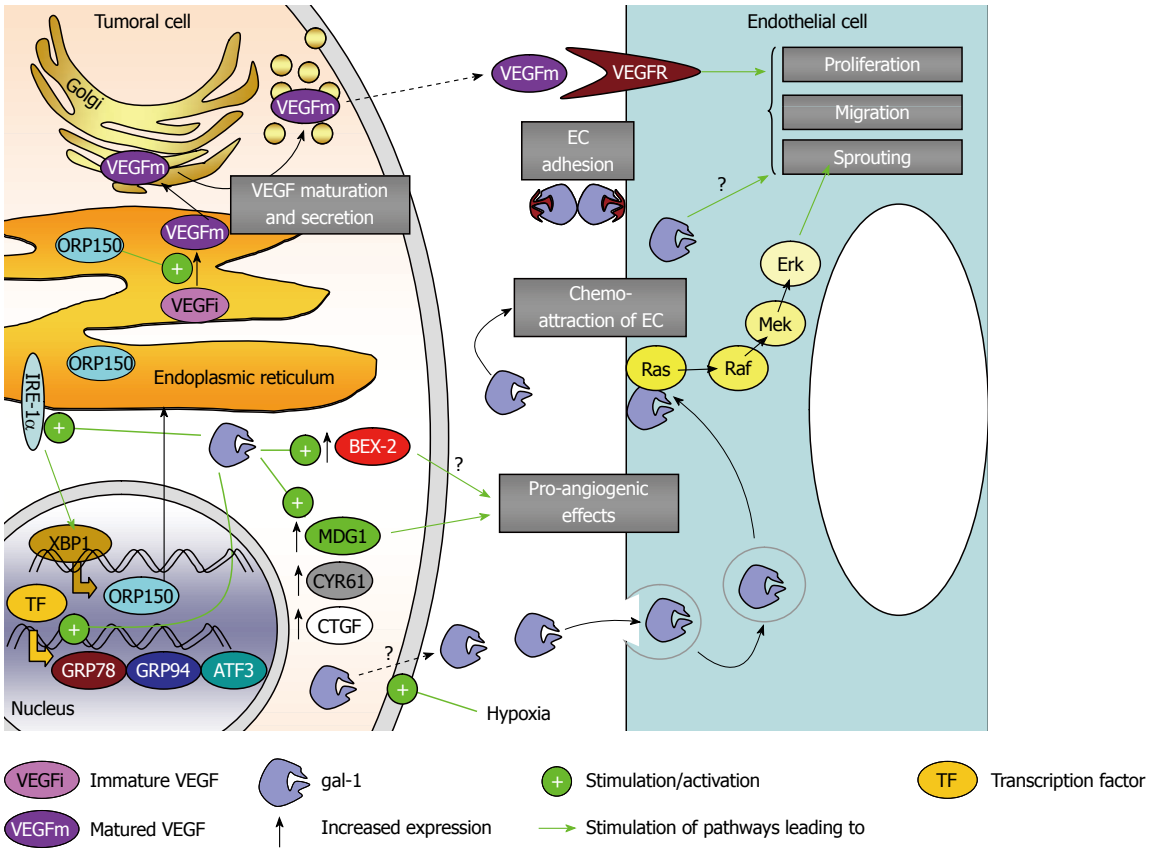

Figure 3 Galectin-1-mediated control of angiogenesis. ATF3: Activating transcription factor 3; BEX2: Brain-expressed X-linked 2; CTGF: Connective tissue growth factor; CYR61: Cysteine-rich angiogenic inducer 61; Erk: Extracellular signal-regulated kinase; GRP78 and GRP94: Glucose-regulated protein 78 and 94; IRE1-α: Endoplasmic reticulum to nucleus signaling 1 α; MDG1: Microvascular endothelial differentiation gene 1; Mek: Mitogen-activated protein kinase kinase; ORP150: Oxygen-related protein 150; Raf: Homolog to murine v-raf leukemia oncogene serine/threonine kinase; Ras: Rat sarcoma virus oncogene protein; TF: Transcription factor; VEGF: Vascular endothelial growth factor; VEGFR: VEGF receptor; XBP1: X-box-binding protein 1. EC: Endothelial cell.

that produce a microenvironment that selects for cells with a more aggressive phenotype[71]. Hypoxia can initiate cell demise by apoptosis/necrosis but can also prevent cell death by provoking adaptive responses that facilitate cell proliferation or angiogenesis, thus contributing to tumor malignant progression[71], and in particular, gliomas[72] and melanomas[53]. Hypoxia is also known to modulate the UPR, a coordinated program that promotes cell survival under conditions of endoplasmic reticulum (ER) stress, which is known to contribute to tumor malignant progression and drug resistance of solid tumors[73]. Considering that galectin-1 is a hypoxia-regulated protein[54,55], we have investigated whether it can interfere with ER stress responses and chemosensitivity. We have examined whether decreasing galectin-1 expression (by means of a siRNA approach) in human Hs683 GBM cells and B16F10 melanoma cells could increase their sensitivity to pro-autophagic or proapoptotic drugs. These data have revealed that temozolomide, the standard treatment for glioma patients, increases galectin-1 expression in Hs683 cells both *in vitro*[36] and *in vivo*[33]. In contrast, reducing galectin-1 expression in these Hs683 glioma cells using siRNA increases the antitumor effects of various chemotherapeutic agents, in particular temozolomide, both *in vitro* and *in vivo*[33,36], which is a feature that we also have observed in experimental melanomas[11]. This decrease in galectin-1 expression in Hs683 glioma cells does not induce apoptotic or autophagic features, but is found to modulate p53 transcriptional activity and decrease p53-targeted gene expression including DDIT3/GADD153/CHOP, DUSP5, ATF3 and GADD45A[36]. Puchades *et al*[74] have demonstrated that galectin-1 expression is negatively regulated by transfection with TP53 in glioma cells. We have further observed that the decrease in galectin-1 expression in glioma cells also impairs the expression levels of seven other genes implicated in chemoresistance: ORP150, HERP, GRP78/Bip, TRA1, BNIP3L, GADD45B and CYR61; some of which are located in the ER and whose expression is also known to be modified by hypoxia[36]. In the case of the B16F10 mouse melanoma model, decreasing galectin-1 expression *in vitro* by means of an anti-galectin-1 siRNA approach does not modify their sensitivity to apoptosis or autophagy[11]. However, it does induce heat-shock-protein-70-mediated lysosomal membrane permeabilization, a process associated with cathepsin B release into the cytosol, which in turn is believed to sensitize the cells to the pro-autophagic effects of temozolomide when grafted *in vivo*[11].

Galectin-1 expression is also upregulated by ionizing

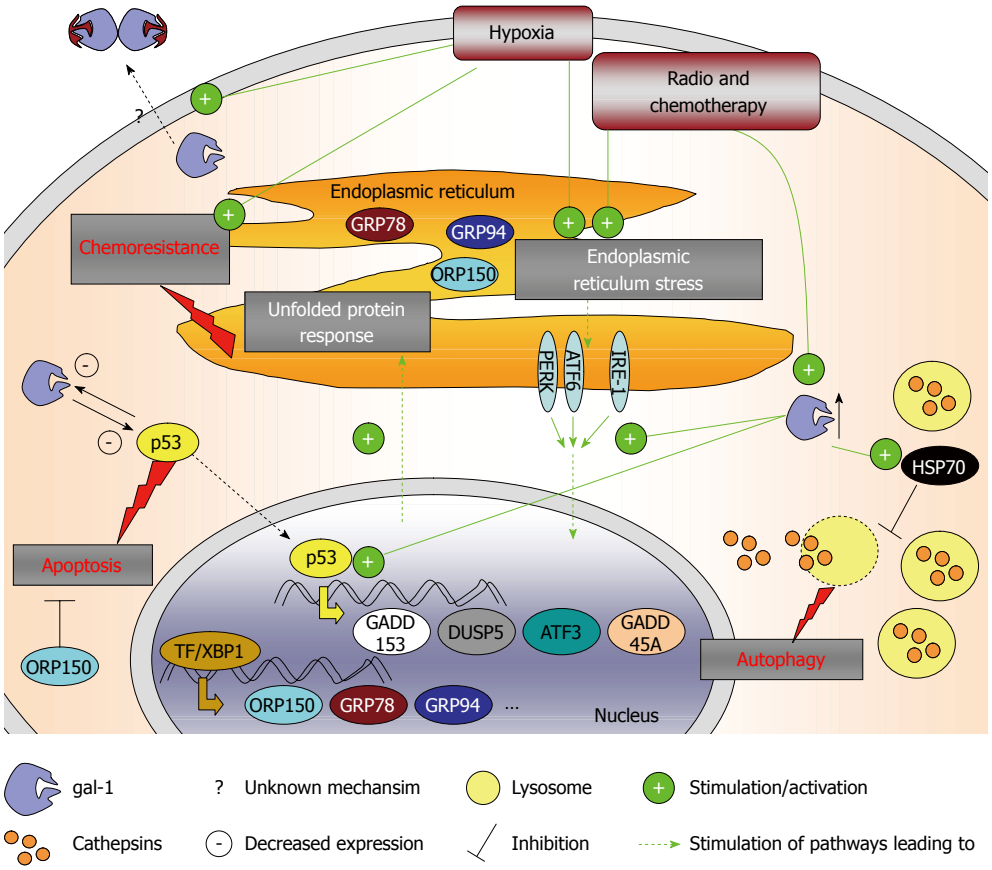

Figure 4 How galectin-1 is involved in chemoresistance of cancer cells. ATF3 and ATF6: Activating transcription factor 3 and 6; DUSP5: Dual specificity protein phosphatase 5; GADD153 and GADD45A: Growth arrest and DNA damage inducible protein 153 and 45 α; GRP78 and GRP94: Glucose-regulated protein 78 and 94; HSP70: Heat shock protein 70; IRE1-α: Endoplasmic reticulum to nucleus signaling 1 α; ORP150: Oxygen-related protein 150; PERK: Protein kinase RNA-like endoplasmic reticulum kinase; TF: Transcription factor; XBP1: X-box-binding protein 1.

irradiation in glioma cell lines[37]. Therefore galectin-1 appears to be induced in cases of various cellular stress stimuli and could promote cell survival through the various mechanisms described above and illustrated in Figure 3.

CONCLUSION

Gliomas and melanomas are associated with dismal prognosis because of their marked intrinsic resistance to proapoptotic stimuli such as conventional chemotherapy and radiotherapy, as well as their capability to escape immune cell attacks. In addition, gliomas and melanomas display pronounced neoangiogenesis. Galectin-1 is a hypoxia-sensitive protein that is abundantly secreted by glioma and melanoma cells, displays marked proangiogenic effects, and provides immunotolerogenic environments to melanoma and glioma cells through the killing of activated T cells that attack these tumor cells. Galectin-1 also protects glioma and melanoma cells against cytotoxic insults (chemotherapy and radiotherapy) through a direct role in the UPR. Altogether, these facts clearly point to galectin-1 as an important target in gliomas and melanomas, to weaken the defenses of these two types of cancers against radiotherapy, chemotherapy and immunotherapy/vaccine therapy, and to reinforce antiangiogenic therapies Figure 4.

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REVIEW

p53 in stem cells

Valeriya Solozobova, Christine Blattner

Valeriya Solozobova, Christine Blattner, Institute of Toxicology and Genetics, Institute of Applied Biosciences, PO-Box 3640, 76021 Karlsruhe, Germany
Christine Blattner, Karlsruher Institute of Technology, PO-Box 3640, 76021 Karlsruhe, Germany
Author contributions: Solozobova V and Blattner C both contributed to this paper; All authors surveyed the literature and contributed to the writing of the article.
Correspondence to: Christine Blattner, PD, PhD, Principal Investigator, Karlsruher Institute of Technology, Institute of Toxicology and Genetics, PO-Box 3640, 76021 Karlsruhe, Germany. christine.blattner@kit.edu
Telephone: +49-721-60822634 Fax: +49-721-60823354
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Abstract

p53 is well known as a "guardian of the genome" for differentiated cells, in which it induces cell cycle arrest and cell death after DNA damage and thus contributes to the maintenance of genomic stability. In addition to this tumor suppressor function for differentiated cells, p53 also plays an important role in stem cells. In this cell type, p53 not only ensures genomic integrity after genotoxic insults but also controls their proliferation and differentiation. Additionally, p53 provides an effective barrier for the generation of pluripotent stem cell-like cells from terminally differentiated cells. In this review, we summarize our current knowledge about p53 activities in embryonic, adult and induced pluripotent stem cells.

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Key words: p53; Embryonic stem cells; Adult stem cells; Induced pluripotent stem cells; Cell differentiation

Peer reviewer: Carlo Ventura, MD, PhD, Full Professor of Molecular Biology, Chief, Laboratory of Molecular Biology and Stem Cell Engineering-National Institute of Biostructures and Biosystems, University of Bologna, S. Orsola-Malpighi Hospital, Cardiovascular Department, Pavilion 21 Via Massarenti 9 Bologna 40138, Italy

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INTRODUCTION

p53 is one of the most well-known and most intensively investigated tumor suppressor proteins. p53 is not a critical protein for survival, as mice and men can develop in the absence of p53 or when the tumor suppressor protein is mutated. The benefit merely comes into play when cells are exposed to conditions that bear an elevated risk of acquiring mutations, such as irradiation or nucleotide deprivation. Then, p53 halts the cell cycle to allow time for repair of damaged DNA, or it initiates a cell death program to eliminate cells with damaged or mutated DNA from the cell population. Functionally, p53 is a transcription factor. After activation, it binds to the promoters of target genes and stimulates transcription of certain genes, while repressing others[1-3]. In addition, p53 can induce apoptosis in a non-transcriptional manner *via* direct interaction with pro- and antiapoptotic proteins[4].

Due to its antiproliferative activity, p53 is under tight control. The rapid degradation of p53 in 26S proteasomes ensures that its abundance in non-stressed cells is low. However, when its activity is required, p53 is protected from degradation and accumulates to high levels, while an array of post-translational modifications fine-tunes its activity[5,6]. The major regulator of p53 abundance is the oncoprotein Mdm2. Mdm2 mediates the polyubiquitination of p53 and its association with 26S proteasomes, resulting in p53 degradation[5,7]. Nonetheless, p53 can also be degraded by other ubiquitin ligases and by ubiquitin-independent pathways[5].

The p53 tumor suppressor protein is part of a multigene family that also includes p63 (TAp63) and p73

(Tap73), as well as several splice variants of these proteins[8]. Although p53, p63 and p73 share a significant degree of homology and regulate a common set of target genes, they target different cellular activities. The p53 protein has a fundamental role in growth control and maintenance of genomic integrity, whereas mice that are deficient in p73 have abnormalities of the nervous system and suffer from chronic infections, and p63-null mice lack limbs and a wide range of epithelial structures[8].

Stem cells are present throughout embryonic development and in adult organs. Basically, there are two types of stem cells: embryonic stem cells (ESCs) that can be isolated from the inner cell mass of blastocysts, and adult stem cells (ASCs) that are found in various tissues and organs. ESCs are pluripotent and can differentiate into all tissues of an embryo, whereas ASCs are more restricted in their differentiation potential. ASCs are, however, vital for the normal turnover of regenerative organs, such as blood, skin or intestine, and they are necessary for replenishing specialized cells when they are lost, for example, after tissue damage[9]. Since extensive proliferation and differentiation of stem cells can contribute to hyperproliferative disorders, a coordinated control of stem cell self-renewal and differentiation is fundamental for maintaining tissue and organ homeostasis. p53 appears to contribute to this restraint by controlling the proliferation, self renewal and differentiation of embryonic and ASCs. With the increasing interest in stem cell biology in the past few years, these activities of p53 have gained significantly more attention. In this review, we provide an overview of the current knowledge on p53 regulation and activity in embryonic, adult and induced pluripotent stem cells.

In the following sections, we distinguish the observations made with murine ESCs (mESCs) or human ESCs (hESCs).

p53 IN ESCs

The first observation about a potential role of p53 in ESCs dates back to 1980 when Mora *et al*[10] observed that *p53* was highly expressed in primary cell cultures obtained from 12-14-d old mouse embryos but not in cells from 16-d old embryos. One year later, they observed that the amount of p53 protein decreased significantly during embryogenesis[11]. This observation was further supported in 1985 when Rogel *et al*[12] noticed a considerable reduction in *p53* mRNA during embryogenesis from day 11 onwards. Six years later, Schmid *et al*[13] reported the tissue-specific expression of the *p53* gene during development and confirmed the strong decline of *p53* mRNA in cells undergoing terminal differentiation. Subsequent publications further substantiated the finding that p53 is highly abundant in mESCs[14,15]. Despite its high abundance and the fact that the tumor suppressor protein was more strongly acetylated at lysine 383 in hESCs compared to differentiated cells, p53 was found to be inactive in stem cells[16,17].

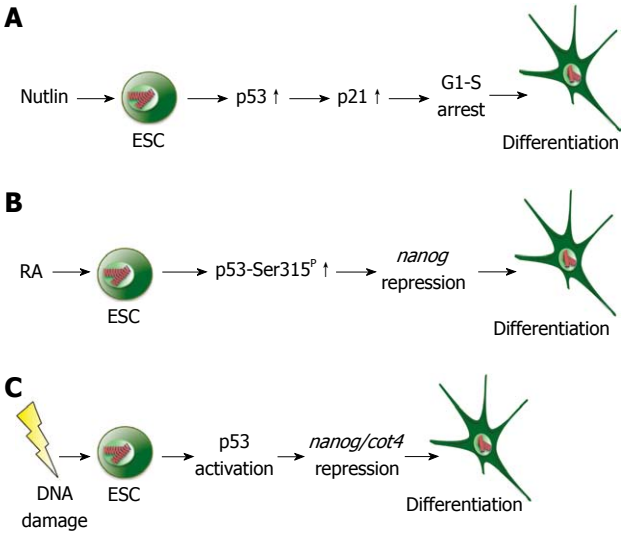

Figure 1 Differentiation of embryonic stem cells by p53. A: Treatment of embryonic stem cells (ESCs) with nutlin leads to p53 accumulation and transcriptional activation. Activated p53 stimulates transcription of *p21*, whose gene product initiates cell cycle arrest at the G1/S border and differentiation; B: Treatment of ESCs with retinoic acid (RA) leads to phosphorylation of p53 at serine 315 and repression of *nanog* followed by differentiation; C: Irradiation of ESCs with UV light or treatment with doxorubicin leads to activation of p53. Activated p53 represses transcription of *nanog* and *oct4*, resulting in the differentiation of ESCs.

During differentiation, p53 protein and RNA decrease significantly[2,11,12,14,15]. Whether the reduction in p53 protein levels also corresponds to reduced activity is an open question. Although Lin *et al*[2] observed an increase in p53 activity during differentiation and transcription of its target genes *p21*, *mdm2* and *killer/DR5,* Sabapathy *et al*[14] observed a conformational change in the tumor suppressor protein, and concomitantly, a decrease in its ability to bind DNA, which would imply a decrease in the transcriptional activity of p53 instead.

In ESCs, p53 is predominantly found in the cytoplasm[18-20], This mainly cytoplasmic localization may also account for the weak activity of this tumor suppressor protein in differentiated cells.

p53 and the proliferation of ESCs

In differentiated cells, p53 is an important regulator of cell proliferation. By controlling expression of the *p21* gene, which encodes a prominent inhibitor of cyclin-dependent kinases, p53 influences transition from G1 into S-phase of the cell cycle[21]. In addition, p53 is able to initiate apoptosis by both the extrinsic and intrinsic pathways[4,22]. In concordance with these activities in differentiated cells, p53 also controls proliferation and cell death in ESCs. Its absence leads to increased proliferation and reduced levels of spontaneous apoptosis of mESCs[14]. Treatment of hESCs with nutlin, an inhibitor of p53 degradation, leads to the rapid accumulation of p21 and to cell cycle arrest at the G1/S boundary[23,24] (Figure 1A). Although removal of the drug after short-term exposure re-establishes normal hESC morphology, extended treatment results in extensive cell death[24].

Table 1 p53 target genes regulating stem cell behavior

Gene	Regulation	Cell type	Effect	Ref.
nanog	Repression	mESCs	Pro-differentiation	[2]
4-Oct	Repression	mESC	Pro-differentiation	[17]
wnt3, wnt3A, wnt 8a, wnt8b, wnt9A, fzd1, fzd 2, fzd6, fzd8, fzd10, lef1	Activation	mESCs	Anti-differentiation	[31]
miRNA-200c	Activation	Mammary epithelial cells	Inhibition of epithelial-mesenchymal transition	[66]
osterix	Repression	Mesenchymal stem cells	Inhibition of osteogenic differentiation	[80]
runx2	Repression	Mesenchymal stem cells	Inhibition of osteogenic differentiation	[81]
pparγ	Repression	Mesenchymal stem cells	Inhibition of adipogenic differentiation	[82]
duoxa1; duox1	Activation	Neural stem cells	Activation of neurogenesis	[100]
gfi1	Activation	Hematopoietic stem cells	Maintenance of quiescence	[117]
necdin	Activation	Hematopoietic stem cells	Maintenance of quiescence	[117]
p21	Activation	Hematopoietic stem cells	Regulation of HSC amount	[117]

Conversely, the inhibition of the transcriptional activity of p53 by pifithrin-α, a small molecule inhibitor of p53, or shifting a temperature-sensitive mutant of p53 to the non-permissive temperature reduces apoptosis in mESCs[14,25,26]. Surprisingly, although pifithrin-α reduces both DNA-damage-induced as well as spontaneous apoptosis in mESCs, treatment of hESCs fails to inhibit apoptosis induction by p53[17]. The reason for this discrepancy is unclear. However, since pifithrin-α only inhibits the transcriptional activities of p53 and not its non-transcriptional proapoptotic activities in the cytoplasm[26], this result may indicate that the mitochondrial pathway of apoptosis induction is more important for p53-dependent apoptosis in hESCs than is the "classical" transcription-dependent pathway.

Role of p53 in the differentiation of ESCs

p53 is a major driving force for the differentiation of ESCs. Spontaneous differentiation of hESCs is significantly reduced when p53 abundance is decreased[17]. The connection between p53 and differentiation became particularly evident when Lin *et al*[2] found that p53 binds to the promoter of *nanog* and suppresses its transcription in mESCs (Figure 1B, Table 1). The homeodomain protein Nanog is highly abundant in ESCs and is required for self-renewal and maintenance of an undifferentiated state[27-29]. Suppression of *nanog* transcription decreases the amount of Nanog protein, and thus, supports ESC differentiation[2]. In addition to the *nanog* promoter, p53 binds to the *oct4* promoter where it also reduces gene transcription[17]. Like Nanog, Oct4 belongs to the group of pluripotency factors that are necessary for maintaining ESCs in an undifferentiated state[27,30]. Treatment of hESCs with nutlin, which is a drug that leads to the strong accumulation of p53, results in decreased *nanog* and *oct4* expression and induction of the differentiation markers *gatA4* and *gatA6*[24].

Further evidence for the importance of p53 for ESC differentiation has come from the analysis of retinoic acid (RA)-mediated differentiation. Treatment with RA is a widely used method for differentiating ESCs in culture. This treatment of ESCs with RA also leads to suppression of *nanog* transcription. Downregulation of *nanog* after treatment with RA is, however, greatly attenuated in ESCs when p53 is genetically deleted, indicating that p53 plays an important role in RA-mediated suppression of *nanog*[2]. It is yet unclear how RA is linked to p53, although the phosphorylation of p53 at serine 315 appears to be particularly important for the suppression of *nanog* transcription (Figure 1B). This phosphorylation enables the recruitment of the corepressor mSin3a to the *nanog* promoter, which is essential for the full suppression of *nanog* transcription[2].

In addition to favoring the differentiation of ESCs, p53 also has antidifferentiation activity. The Wnt signaling pathway is extremely important for the maintenance of self-renewal and pluripotency of murine and human ESCs[31,32]. Wnt signaling is activated by binding of Wnt-ligands to their cognate Frizzled receptor, which culminates in the activation of the Lef1/Tcf transcription complex[33]. Activation of p53 also counteracts differentiation by leading to the induction of Wnt ligands and receptors and Lef1[34] (Table 1).

p53 activities in ESCs in response to DNA damage

In differentiated cells, DNA damage leads to the accumulation of p53 in the nucleus and mitochondria and to the transcription of its target genes, including *mdm2*, *p21*, *bax*, *puma* and *noxa*, followed by cell cycle arrest at the G1/S boundary and initiation of cell death[35]. Although the elevated abundance of p53 in ESCs is generally accepted, there are contradictory reports about its activity in ESCs in response to DNA damage. Some studies have reported that p53 is only weakly or not activated in response to γ-irradiation of mESCs, or after treatment with *n*-phosphonacetyl-L-aspartate, and that both its protein level and expression of its target genes *p21* and *mdm2* should remain unchanged. Other studies, including our own, have reported p53 accumulation in the nucleus of mESCs in response to UV light or γ irradiation, or after treatment with doxorubicin, as well as transcriptional activation of its target genes *p21*, *mdm2*, *puma* and *noxa*[2,16,18,36].

Despite transcription of the *p21* gene after p53 activation, no p21 protein is produced in mESCs[18,37,38]. For hESCs, there are conflicting data regarding p53 activity in response to DNA damage. Qin *et al*[17] failed to observe

an increase in *p21* mRNA in response to UV irradiation despite accumulation and phosphorylation of p53, whereas Filion *et al*[39] reported a significant induction of *p21* mRNA in response to ionizing radiation. However, as reported in mESCs, the p21 protein was hardly detectable in hESCs.

Similar to differentiated cells in which p53 halts the cell cycle and drives cells with damaged DNA into apoptosis[40], p53 is regarded as being responsible for the high sensitivity of mESCs to DNA damage. Following its accumulation in response to UV irradiation, p53 rapidly induces apoptosis in mESCs, leading to the death of a majority of the cells[18,41]. Treatment of hESCs with etoposide leads to association of p53 with mitochondria and to increased expression of *puma*. Subsequently, Bax and Mcl1 are co-localized in perinuclear structures that resemble mitochondrial aggregates, followed by rapid and extensive induction of apoptosis[20]. hESCs stably transduced with an shRNA that is targeted against p53 show significant reduction of *bax* and *puma* expression and apoptosis after treatment with etoposide, indicating a requirement of p53 for the induction of cell death in hESCs in response to DNA damage[20]. In mESCs, the colony forming ability after UV irradiation is more strongly reduced in p53-positive mESCs than in those that lack the tumor suppressor protein[41]. Most interestingly, although ESCs rapidly undergo apoptosis in response to UV-irradiation or treatment with etoposide, ionizing radiation is less efficient in inducing cell death. Conflicting observations have, however, been made regarding the regulation of the clonogenic potential by p53 after ionizing irradiation. Corbet *et al*[41] have observed a stronger reduction in the colony forming ability of p53-positive mESCs after γ irradiation in comparison to p53-deficient mESCs, although we failed to observe this difference after ionizing radiation[18].

Apart from the increase in abundance, the p53 protein is also post-translationally modified in response to DNA damage[5]. Of note, these post-translational modifications differ between ESCs and differentiated cells and between hESCs and mESCs, both in quality and in intensity. In response to UV- or ionizing radiation, p53 from hESCs is barely phosphorylated at serine 9, which is an amino acid that is phosphorylated in response to cellular stress in differentiated cells[42]. Also, phosphorylation of serine 20 (serine 23 of murine p53) is rather weak in mESCs. One explanation for this weak phosphorylation of p53 in mESCs is that Chk2, the kinase that usually phosphorylates this site, is hyperphosphorylated and tethered in aggregates in mESCs, thus limiting its availability for phosphorylating its cellular targets[37,43]. Conversely, phosphorylation on serine 15 (serine 18 of murine p53) of p53 is stronger in hESCs than in differentiated human cells, while its intensity is similar in mESCs and mouse embryonic fibroblasts (MEFs)[17,37].

In contrast to differentiated cells in which damage-induced p53 activities are mostly restricted to the induction of cell cycle arrest and apoptosis, p53 activation also affects differentiation in ESCs as a response to DNA damage. By binding to the promoters of *oct4* and *nanog*, p53 represses the transcription of these pluripotency factors and facilitates the differentiation of damaged ESCs[2,17,19] (Figure 1C). However, p53 can also induce transcription of Wnt ligands and receptors in response to DNA damage, which has antidifferentiation properties[34,44].

Overall, by enhancing the sensitivity to DNA damaging agents, induction of cell death and by encouraging differentiation, p53 acts as a guardian of the genome for ESCs despite its failure to induce G1 arrest in this cell type.

p53 IN ASCs

In addition to the developing embryo, stem cells have also been identified in somatic tissues of adults, including the nervous system, bone marrow, epidermis, skeletal muscle, mammary gland and liver[45-51]. Stem cells in somatic tissue are usually called tissue or ASCs in order to distinguish them from ESCs that are derived from the inner cell mass of blastocysts[52]. Even in adult organs, tissue stem cells retain the potential for self-renewal and differentiation into different cell types, but they have lost pluripotency as well as the capacity to form a complete new organism[53]. In organs, ASCs reside in specific niches where they remain in a quiescent state during most of the host's lifetime. However, when new cells are required, these tissue stem cells divide postnatally, frequently in an asymmetric way, by which they generate another stem cell as well as a committed progenitor daughter cell. The progenitor cell then proliferates further and produces a pool of differentiated cells. These differentiated cells replenish cells as they die, due to natural wearing away or after injury[54,55]. Therefore, stem cells are intimately involved in maintaining tissue homeostasis.

Similar to ESCs, proliferation, self-renewal and genomic stability are tightly controlled in ASCs. Defects in these parameters contribute to premature aging, to failure to repair tissue injury and to the development of cancer[56-59]. Detailed knowledge about the processes that regulate proliferation, self-renewal and transformation of tissue stem cells is therefore crucial to enable safe usage of these cells for stem-cell-based therapies. The tumor suppressor protein p53 is a key regulator of these processes. In the following sections, we highlight the most important results regarding p53 regulation and function in various types of tissue stem cells.

Mammary gland stem cells

Mammary gland stem cells (MGSCs) direct mammary gland development and functionality, and alterations in the proliferation of these cells result in defects of the mammary gland[51,60-62]. p53 appears to be a critical control component for the development of mammary glands. This appearance became particularly evident when mammary glands of mice that expressed one wild-type and one C-terminally deleted allele of p53 were

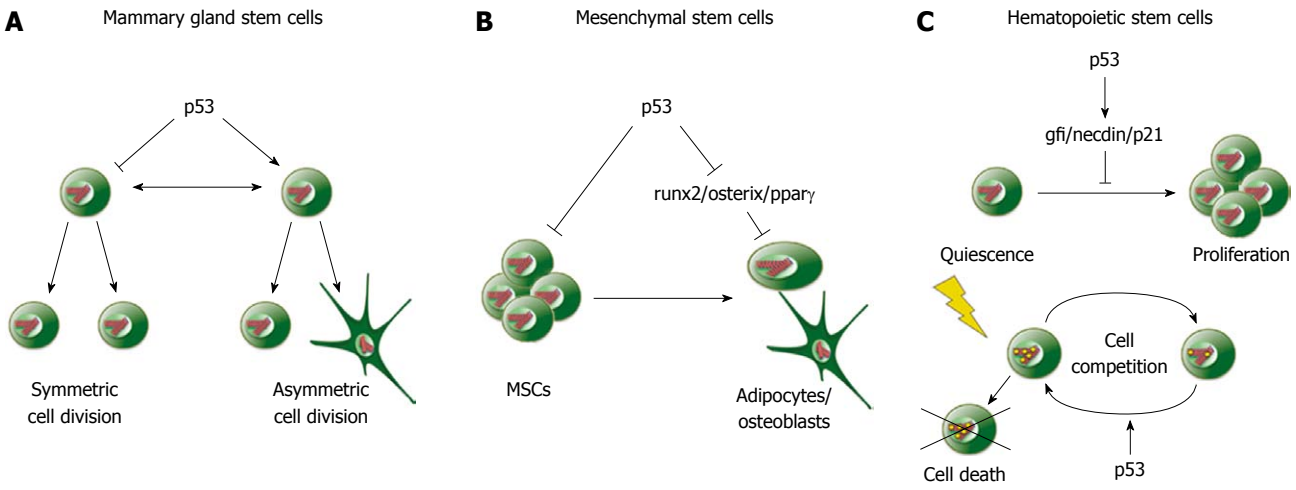

Figure 2 p53 suppresses self-renewal and promotes differentiation of adult stem cells. A: In mammary gland stem cells, p53 promotes asymmetric cell division, resulting in an increased number of differentiated cells and a reduction in the stem cell pool; B: In mesenchymal stem cells (MSCs), p53 suppresses proliferation and self-renewal and reduces differentiation by suppressing runx2, osterix and pparγ; C: p53 supports quiescence of hematopoietic stem cells and reduces proliferation. This effect is mediated by transcriptional activation of *gf1*, *necdin* and *p21* (Top). In response to DNA damage, p53 enhances the death of severely damaged cells by cell competition (below).

investigated[63]. Expression of a C-terminally deleted allele of *p53* in combination with a wild-type allele confers increased resistance to tumorigenesis and accelerated aging in mice[64]. Mice that express this combination of wild-type and C-terminally deleted *p53* show significant defects in the morphogenesis of mammary gland ducts. Moreover, when mammary epithelium from these mice is serially transplanted, the epithelium shows severely reduced transplant capabilities, indicative of early stem cell exhaustion[63]. Conversely, mammary epithelium of mice, where p53 is genetically deleted, contains an increased number of stem cells and is highly susceptible to tumor formation[65,66]. Moreover, MGSCs from $p53^{-/-}$ mice produce a higher number of mammospheres that are larger in size when cultured[67]. Mammary stem cells from $p53^{+/-}$ mice also show a higher number of mammospheres than those from $p53^{+/+}$ mice, indicating that gene dosage of p53 is important for proliferation[67]. These results strongly suggest that p53 controls the maintenance of a constant number of MGSCs by probably stimulating asymmetric cell division[66] (Figure 2A). Loss of the tumor suppressor protein shifts proliferation to the symmetrical division of MGSCs, resulting in the production of only stem cells that all retain pluripotency and self-renewal capacity. This symmetric division of MGSCs results in significant enlargement of the stem cell pool, which favors tumorigenesis of the mammary gland[66,67].

In addition to controlling proliferation and symmetry of MGSC division, p53 regulates epithelial-mesenchymal transition (EMT) in the mammary gland. EMT and the reverse process, mesenchymal-epithelial transition (MET), are key processes for the regulation of embryogenesis. EMT and MET are a series of events during which epithelial or mesenchymal cells lose many of their characteristics and take on properties that are typical of the other cell type. This transition occurs as a result of a number of intercellular and intracellular adjustments[68]. p53 suppresses EMT by binding to the promoter of the microRNA *miR-200c* and activating its expression[69] (Table 1). miR-200c is a microRNA that regulates EMT by inhibiting ZEB1/2, a transcriptional repressor of E-cadherin[70]. Re-expression of miR-200c in stem cells with deleted p53 reduces formation of mammospheres, indicating that the control of proliferation and asymmetric cell division of MGSCs by p53 may primarily occur by regulating this microRNA[69].

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) reside in the bone marrow and can differentiate into different types of cells of mesodermal origin, such as osteoblasts, adipocytes and chondrocytes[71]. Multipotent bone marrow MSCs express low levels of adipogenic and osteogenic factors. When this balance of adipogenic and osteogenic factors is tipped, cells become committed toward one of these lineages, and lineage-specific transcription factors that promote one particular cell fate are transcribed. Lineage-specific transcription factor activation usually occurs concomitantly with repression of the other cells' fate[72]. Loss of p53 in MSCs results in severe alterations of tissue homeostasis. The complete absence of p53 promotes a higher proliferation rate of bone-marrow-derived MSCs, which acquire the typical MSC surface phenotype earlier than wild-type MSCs do. In addition, more precursors are generated that are able to form colonies.

MSCs can be isolated and expanded *in vitro*, which predestines these cells for tissue engineering and therapeutic applications[73-75]. However, MSCs that have been extensively propagated *in vitro* frequently acquire mutations that may lead to spontaneous transformation[57,76,77]. Therefore, extensively propagated MSCs should be taken with care with regard to patient therapy. Moreover, the expression profiles and mutation spectra of p53 of these extensively propagated MSCs are similar to those found

in human tumors. Therefore, these findings raise the conjecture that mesenchymal tumors may originate from aged MSCs[78]. The coincidence of *p53* mutations and the development of tumors in aged MSCs suggests that p53 activity might be required for maintaining genomic stability in this cell type, and for suppression of spontaneous transformation in long-term MSC cultures[77]. This notion is further supported by the observation that MSCs from mice with a genetic deletion of both *p53* alleles are capable of forming tumors when they are injected into immunodeficient mice[79]. Conversely, when both alleles of the *p21* gene, a target gene of p53 that is mainly responsible for p53-mediated cell cycle arrest, are deleted, MSCs do not show any signs of tumoral transformation[80,81]. Only when at least one allele of *p53* is mutated in addition to *p21* does *p53* expression become lost after long-term culture, and a significant increase in growth rate and genomic instability is observed[82]. Loss of p53 expression is further accompanied by the loss of expression of the cdk inhibitor *p16*, upregulation of $p19^{Arf}$ and *c-myc*, and by the complete loss of any senescence phenotype[82].

In addition to controlling proliferation and transformation, p53 also influences the differentiation of MSCs (Figure 2B). MSCs that lack p53 generally differentiate into adipocytes or osteocytes more rapidly than wild-type MSCs. This increased differentiation occurs along with enhanced expression of osteoblast differentiation factors *osterix* and *runx2,* which are normally repressed by p53, and by increased expression of *runx2* and *pparγ*[83-85] (Table 1). Conversely, osteoblast progenitor cells with elevated p53 activity show reduced proliferation and reduced differentiation, indicating that p53 may negatively regulate the differentiation process[84]. Accelerated differentiation in combination with an increase in macrophage colony-stimulating factor is thought to be the reason for the high bone mass that is observed in the absence of p53[83].

Neural stem cells

The nervous system develops from neural stem cells (NSCs), which have the capacity to self-renew and differentiate into neurons, oligodendrocytes and astrocytes[86,87]. Proliferation and differentiation of the nervous system of mammals is limited after birth, although certain areas in the brain retain multipotent precursor cells with the ability to self-renew and differentiate along neural lineages. Neurogenesis in the adult brain has been particularly observed in the subventricular zone (SVZ) of the lateral ventricle and in the subgranular zone of the hippocampus[88].

p53 has emerged as an important regulator of cell division both in the developing and in the adult brain[89-93]. The tumor suppressor protein has been shown to be expressed in the SVZ as well as the lateral ventricle wall, where most of the glial-fibrillary-acidic-protein-positive astrocytes and Musashi1-positive progenitor cells of the SVZ reveal p53 immunoreactivity[90]. The major function of p53 in the brain is to protect neurons from DNA damage and transformation. Accordingly, p53 induces cell-cycle arrest, DNA repair and cell death in the brain in response to genotoxic insults. In addition, p53 regulates proliferation, differentiation and development of the brain. It promotes neuronal maturation, axon outgrowth and regeneration after injury, and has a crucial role in eliciting neuronal cell death during development[94].

The first indication that p53 might regulate NSC proliferation came about 15 years ago when the *p53* gene was deleted in mice. Of those animals that lacked both alleles of p53, more than 15% showed cellular overgrowth in the mid-brain[95]. Comparisons of wild-type and p53 knockout mice have revealed that the number of proliferating cells in the SVZ from p53-null mice is significantly higher than in p53 wild-type mice. This hyperproliferation of cells of the SVZ results in areas of increased cell density that are distributed along the walls of the lateral ventricle[90,91]. The hyperproliferation of cells of the SVZ is probably caused by expansion of the stem cell/progenitor compartment, along with rapid differentiation towards neuronal and glial lineages[90,91]. An increased proliferation of p53-negative NSCs becomes apparent when NSCs from p53 knockout mice are taken into culture. These NSCs form an increased number of clonal aggregates called neurospheres in comparison to those from wild-type mice. In addition, neurospheres from p53-null NSCs are larger in size, due to increased cell content[90,91]. When NSCs are recovered from these neurospheres, a greater proportion of cells are capable of initiating new neurospheres compared to NSCs from wild-type mice[90,91]. These observations strongly suggest that p53 is a negative regulator of NSC self-renewal.

Proliferation of NSCs lacking p53 is further enhanced when cells are also null for phosphatase and tensin homolog (PTEN). Moreover, although NSCs that lack p53 still respond to differentiation cues, this property is not the case when PTEN and p53 are both genetically deleted. Instead, the cells retain their stem-cell-like morphology and continue to express NSC lineage markers, even after experiencing differentiation cues[96]. The reason for this increased proliferation and inhibition of differentiation is probably a substantial increase in *c-myc* expression in the absence of p53 and PTEN, whereas *c-myc* expression is only marginally elevated in $p53^{-/-}$ or $PTEN^{-/-}$ NSCs. Enforced expression of *c-myc* in $p53^{-/-}$ NSCs also enhances proliferation and represses differentiation in the absence of p53 alone, whereas genetic deletion of *c-myc* in p53/PTEN-deficient NSCs restores their differentiation potential[96]. Thus, p53 and PTEN may both suppress *c-myc* expression in NSCs and allow differentiation to take place. Loss of one of these proteins may be compensated by the other factor or other components in the cell, while loss of both leads to snapping through of the differentiation-blocked phenotype.

Alterations in cell number can be achieved by modulating proliferation or by enhancing or reducing cell death. p53 can affect both possibilities; it influences cell proliferation by controlling expression of the cdk-

inhibitor *p21*, and cell death by activating transcription of proapoptotic genes such as *bax*, *puma* or *noxa*, as well as by binding to pro- and antiapoptotic members of the Bcl-2 family[3,4]. Yet, the ability of p53 to induce cell death appears to be negligible for constraining proliferation of NSCs. The smaller neurospheres that are formed in the presence of p53 show no indication of cell death. Also, overexpression of an isoform of p53 (ΔNp53) that is shorter and more stable, and therefore, more active, reduces the size of neurospheres but does not increase the level of apoptosis[97-99]. Consistent with these *in vitro* results, mice overexpressing ΔNp53 show a clear age-dependent decline in the number of proliferating cells in the SVZ, and a reduction in the supply of new olfactory bulb neurons compared to mice expressing normal p53. Olfactory bulb neuron exhaustion is not apparent in younger mice, indicating that it is caused by premature NSC exhaustion[99]. In line with the reduction in NSC proliferation and the absence of increased cell death, overexpression of ΔNp53 leads to constitutive expression of the cdk-inhibitor *p21*, compromises the re-entry of dormant NSCs into the cell cycle and to extended durations of cell-cycle passages[99].

Although there is unanimity about the regulatory role of p53 in NSC proliferation, there are differing reports regarding the impact of p53 for differentiation. Jonas Meletis *et al*[90] have reported that neurospheres from p53-null and wild-type NSCs contain a similar number of neurons, astrocytes and oligodendrocytes, whereas Armesilla-Diaz *et al*[89] and Masato Nagao *et al*[100] have found that differentiation of neurospheres from p53-null mice is biased towards neuronal precursors. Regardless of the differing reports regarding the role of p53 in NSC differentiation, p53 activity increases during development and is at the time when neuronal differentiation takes place at its maximum[101,102]. Also in cultured NSCs, p53 expression increases during differentiation[103], which might be caused by a gradual upregulation of $p19^{Arf}$. $p19^{Arf}$ binds to the central domain of the Mdm2 , which is the most important negative regulator of p53, and inhibits Mdm2-mediated degradation of the tumor suppressor protein[5]. As a result of this inhibition, p53 accumulates in the cell in an Arf-dose-dependent manner. The amount of $p19^{Arf}$ increases up to 20-fold from E13.5 to postnatal day 2, which could be responsible for the increase in p53 expression[100]. Consistent with a regulation of p53 by $p19^{Arf}$ and a putative role of p53 in suppressing self-renewal of NSCs and supporting differentiation towards glia cells, early-stage NSCs, which express little $p19^{Arf}$, retain a high self-renewal capacity and differentiate towards the neurogenic lineage, whereas late-stage NSCs, which possess more $p19^{Arf}$, have a lower self-renewal capacity and predominantly generate glia cells[100]. In line with this notion, the enhanced downregulation of $p19^{Arf}$ or genetic deletion of *p53* enhances the self-renewal potential of NSCs as well as the production of neurons, whereas overexpression of $p19^{Arf}$ reduces NSC proliferation and promotes differentiation into glia cells[100] (Figure 3). Furthermore,

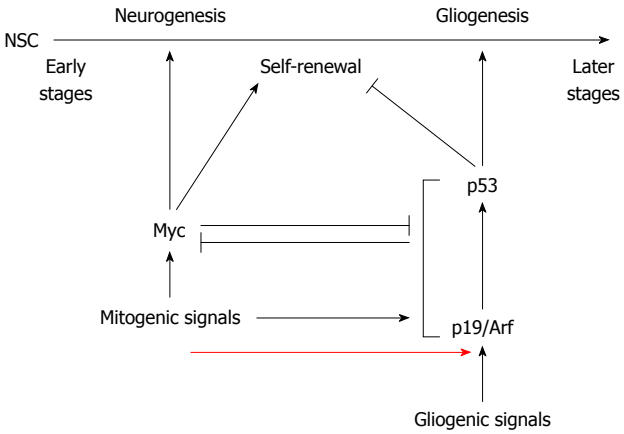

Figure 3 Antagonistic regulation of differentiation of neural stem cells by Arf/p53 and Myc. Myc regulates self-renewal of neural stem cells (NSCs) and enhances their differentiation into the neuronal lineage. At early stages of embryogenesis, *myc* expression is high and $p19^{Arf}$ expression is low. Later in development, mitogenic signals upregulate $p19^{Arf}$ expression, resulting in enhanced abundance of the p53 tumor suppressor protein, which suppresses self-renewal of NSCs and differentiation towards the neuronal lineage while it supports gliogenesis [100].

induction of NSC differentiation leads to phosphorylation of p53 at serine 15 and enhances its DNA binding activity. It is, therefore, not surprising that differentiation of NSCs is concurrent with alterations in the expression of p53 target genes[104]. Two possible target genes of p53 during neuronal differentiation are dual oxidase (*DUOX1*) and its maturation factor *DOUXA1* (Table 1). Expression of *p53* in P19 pluripotent embryonal carcinoma cells increases the level of both DUOX1 and DUOXA1 and allows their physical interaction[103]. Both proteins, DUOX1 and DUOXA1, play an important role in the regulation of neuronal differentiation through DOUX1-mediated reactive oxygen species production and modulation of intermediate filaments[105]. Transcriptional activation of these two proteins may, therefore, contribute to the differentiation-inducing activity of p53 in NSCs.

About 50% of human tumors express a mutated *p53* gene, including brain tumors, where p53 mutations are found frequently. Mutations of p53 are associated with both tumor initiation and expansion in the brain, supporting the importance of this tumor suppressor protein for maintaining tissue homeostasis[106]. In differentiated cells, the activity of p53 comes mainly into play when the DNA of a cell has been damaged, at which point p53 initiates cell cycle arrest and cell death[107]. More recently, it has been shown that when cell cycle regulation or DNA integrity is perturbed in neural precursors, p53 is a major proapoptotic protein[108]. Telencephalic cells grown to neurospheres are arrested at the G1/S boundary of the cell cycle after irradiation, and show enhanced induction of apoptosis along with enhanced abundance and nuclear localization of p53 and its downstream targets p21 and Bax. At the same time, *Rad51* and *Rrm2* are transcriptionally repressed by p53, demonstrating that in response to genotoxic stress, p53 regulates transcription and repres-

sion of its target genes in neural progenitors[89,109,110]. Cultures from $p53^{-/-}$ neural progenitors are not arrested in G1/S phase and exhibit a significantly lower level of spontaneous and DNA-damage-induced apoptosis than their wild-type counterparts, thereby showing that DNA damage-induced G1 arrest and apoptosis in neural precursor cells are critically dependent on p53[89,109,110]. Also, immortalized human NSCs show upregulation and phosphorylation of p53 in response to ionizing radiation[111], indicating that this is a general response of NSCs to DNA damage. Importantly, although neurospheres derived from wild-type animals exhibit only slight karyotypic modifications, neurospheres derived from p53-null animals show major structural chromosomal aberrations and aneuploidy, particularly with higher passage numbers[89], demonstrating that p53 is required for the maintenance of chromosomal stability in NSCs.

Hematopoietic stem cells

Most adult hematopoietic stem cells (HSCs) exist in a relatively quiescent state in the microenvironment of the bone marrow. Once activated, they start to proliferate and differentiate along the different hematopoietic cell lineages[112,113].

As shown for stem cells in other tissues, p53 activity also affects cell number, proliferation potential and differentiation of HSCs. Accordingly, HSCs of mice with a hyperactive mutant form of p53[64] show a reduced number of proliferating HSCs. Conversely, a reduction in p53 increases proliferation and self-renewal of HSCs[114-116]. Absence of the p53 target gene *p21*[117] (Table 1) results in an increased number of HSCs, whereas high levels of p21 mRNA in the quiescent stem cell fraction restrict stem cells from entry into the cell cycle[118]. Nevertheless, it should be noted that p21 abundance is also regulated by mechanisms independent of p53[119].

In addition to controlling proliferation of HSCs, p53 is an essential component for maintaining quiescence of HSCs[120]. This activity of p53 may also be regulated by p21[118], although others have found that the role of p21 in maintaining HSC function is limited[115,121]. Other p53 target genes that might be involved in mediating quiescence are *gfi-1* and *necdin* (Figure 2C). Both genes have been identified as direct p53 targets by transcript profiling[115] (Table 1). Gfi-1 is a zinc-finger-containing repressor protein that has been shown in the past to restrict HSC proliferation[122,123]. Necdin is a growth-inhibitory protein that interacts with multiple proliferation-promoting proteins, such as simian virus 40 large T antigen or E2F-1[124-126]. Downregulation of Necdin diminishes HSC quiescence, whereas quiescence is increased when *necdin* is overexpressed[115].

Furthermore, p53 is an important component of the DNA damage response of HSCs. HSCs from mice lacking p53 are more resistant to irradiation-induced apoptosis compared to HSCs from wild-type mice, indicating that p53 induces cell death in HSCs in response to DNA damage[115]. p53 also controls a process called cell competition in HSCs in response to DNA damage (Figure 2C). Cell competition is the active elimination of suboptimal cells, basically enabling the selection of the fittest. This process has initially been described for *Drosophila*, but it probably plays a wider role in tissue homeostasis of all metazoans[127]. Cell competition is activated in HSCs after DNA damage and selects for the least-damaged cells. Despite being controlled by p53, cell competition is distinct from the classical p53-mediated DNA damage response. It persists for several months, appears to be specific for HSCs and progenitor cells, and depends on relative rather than absolute p53 levels in competing cells. Cell competition in response to DNA damage is probably mediated by a non-cell-autonomous induction of proliferation arrest and senescence-related gene expression in those cells that possess higher p53 activity[128].

p53 IN INDUCED PLURIPOTENT STEM CELLS

Somatic cells can be reprogrammed into pluripotent stem cell-like cells by overexpression of combinations of different pluripotency factors. The reprogramming of differentiated cells is a possible source for autologous pluripotent cells that can be transplanted into patients.

Since 2006, when the first induced pluripotent stem cells (iPSCs) were generated by overexpression of *oct4*, *sox2*, *klf4* and *c-myc* in adult and embryonic fibroblasts[129], iPSCs have been generated from cells of multiple origins, including embryonic fibroblasts, adult fibroblasts, neural progenitor cells, hepatocytes, epithelial cells and keratinocytes, by combinations of different reprogramming factors[130,131]. However, the low frequency and the tendency to induce malignant transformation by overexpression of proto-oncogenes raises doubts about the clinical applicability of this approach.

Reprogramming only occurs in a very small percentage of transfected cells, suggesting the existence of reprogramming barriers. Since decreased protein levels of p53 and p21 were observed in iPSCs derived from MEFs[129], it was assumed that p53 might play a role in the reprogramming process of somatic cells. One of the first such reports came from Zhao *et al*[132] who have observed that downregulation of p53 by siRNA dramatically enhances the efficiency of iPSC generation from human adult fibroblasts. This result has been confirmed by Kawamura *et al*[133] and Li *et al*[134], who have observed that reducing p53 levels by p53 shRNA or by using *p53*-null MEFs increases the efficiency of reprogramming, whereas re-expression of p53 in *p53*-null MEFs markedly reduces it. Downregulation of $p19^{Arf}$, a prominent regulator of p53 activity[5], also enhances reprogramming efficiency of MEFs and murine keratinocytes[134]. The reprogramming efficiency of mouse fibroblasts lacking $p19^{Arf}$ is similar to that of MEFs lacking *p53*, suggesting that the reprogramming barrier that is controlled by $p19^{Arf}$ is mediated by p53[134] (Figure 4). However, despite the leading role of p53 for reprogramming of human cells, $p19^{Arf}$

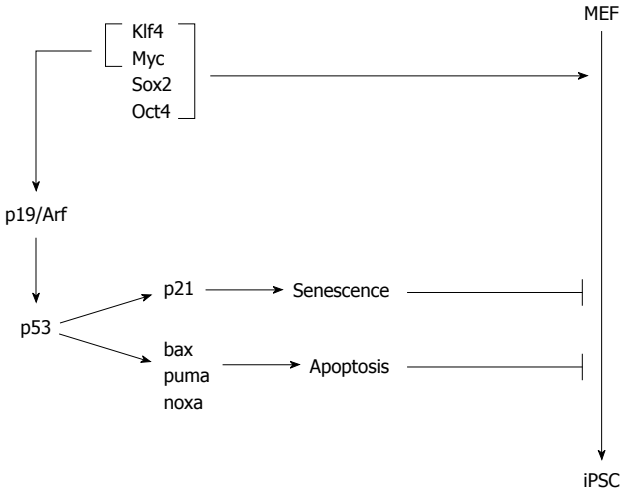

Figure 4 p53 provides a barrier for the reprogramming of somatic cells to induced pluripotent stem cells. Somatic cells, such as mouse embryonic fibroblasts (MEFs), can be reprogrammed to induced pluripotent stem cells (iPSCs) after overexpression of a combination of reprogramming factors, such as Klf4, Sox2, Myc and Oct4. Klf4 and Myc induce $p19^{Arf}$ expression, which prevents p53 degradation, resulting in its accumulation and expression of its target genes. Among the target genes of p53 is *p21*, which causes senescence, and *bax*, *puma* and *noxa*, which lead to apoptosis.

appears to be more important for murine cells[132,134]. It is presently unclear how and why p53 imposes a reprogramming barrier. One possible explanation is that the reprogramming factors c-Myc, Oct4 and Sox2 induce p53 activity, thus, eliciting a stress response that finally leads to cell cycle arrest and/or cell death (Figure 4). This assumption is further supported by the finding that overexpression of the antiapoptotic gene *bcl-2* increases the efficiency of reprogramming, indicating that p53 implements the reprogramming barrier by eliminating cells that express the reprogramming factors by apoptosis[133]. Most interestingly, when p53 levels are reduced, MEFs can be reprogrammed to pluripotency in the absence of oncogenes, such as *c-myc* or *klf4*, simply by the overexpression of *oct4* and *sox2*[133]. Moreover, in the absence of *p53*, up to 10% of transduced cells became iPSCs, and iPSCs can even be generated from terminally differentiated lymphocytes[135]. p53 may also implement a barrier for reprogramming by inducing senescence. Expression of the four reprogramming factors *oct4*, *sox2*, *klf4* and *c-myc* triggers a senescence-like phenotype in human fibroblasts[136] (Figure 4). Senescence is an irreversible cell cycle arrest in the G1 phase of the cell cycle caused, for example, in response to cellular stress, such as DNA damage, treatment with chemotherapeutic drugs, or aberrant expression of oncogenes. This arrest occurs mainly through the activation of p53 and upregulation of $p16^{INK4}$ and p21[137]. In fact, *p21* has been shown to be an important target of p53 in the context of implementing a reprogramming barrier[135]. Nevertheless, other target genes of p53 also appear to contribute, as the absence of *p21* enhances reprogramming efficiency by only about fourfold, whereas the absence of p53 does so by 7-10-fold[134,135]. Transfection of somatic cells with the four reprogramming factors significantly increases the percentage of cells arrested in G1 phase without inducing apoptosis, indicating a possible involvement of p21. Moreover, cells expressing the reprogramming factors display an enlarged cytoplasm, a senescence-associated β-galactosidase activity and heterochromatic foci. Ablation of the senescence effectors, $p16^{INK4a}$, p53 and p21 improves the efficiency of reprogramming significantly[136].

Although suppression of p53 appears to be a feasible way of improving reprogramming efficiency, permanent suppression of p53 may lower the quality of iPSCs, by allowing the outgrowth of iPSCs with permanent DNA lesions and chromosomal aberrations. p53 appears to be critically involved in preventing the reprogramming of cells with damaged DNA, short telomeres or reduced DNA repair deficiency. MEFs with critically short telomeres or MEFs treated with low doses of γ-irradiation or UV light show low reprogramming efficiency. Abrogation of p53 in these cells restores reprogramming efficiency to the level of undamaged *p53*-null cells[138].

CONCLUSION

Although mice with genetic deletions of both *p53* alleles develop normally, there is increasing evidence for a role of p53 in the regulation of stem cell proliferation, differentiation and the maintenance of stem cell genetic stability. At present, we are only beginning to understand the different actions that p53 exerts in stem cells, and the underlying mechanisms are even less clear. It is of particular interest to establish how p53 avoids the acquisition of mutations and genomic alterations after prolonged propagation of ASCs *in vitro*. Another important question is why p53 implements a barrier for the generation of iPSCs and how to circumvent this barrier for the generation of isotypic stem cells from patients without instigating the risk of expanding stem cells with genetic alterations. Transient suppression of p53 might be a useful compromise, however, it is presently unclear whether cells that survive the reprogramming process are truly free of mutations and aberrations when p53 has been inactivated for some duration. Therefore, more research is required to allow the safe use of stem cells for therapy.

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Acknowledgments to reviewers of *World Journal of Biological Chemistry*

Many reviewers have contributed their expertise and time to the peer review, a critical process to ensure the quality of *World Journal of Biological Chemistry*. The editors and authors of the articles submitted to the journal are grateful to the following reviewers for evaluating the articles (including those published in this issue and those rejected for this issue) during the last editing time period.

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Carlo Ventura, MD, PhD, Full Professor of Molecular Biology, Chief, Laboratory of Molecular Biology and Stem Cell Engineering-National Institute of Biostructures and Biosystems, University of Bologna, S. Orsola-Malpighi Hospital, Cardiovascular Department, Pavilion 21 Via Massarenti 9 Bologna 40138, Italy

Ming Zhang, PhD, Associate Professor, Department of Molecular Pharmacology and Biological Chemistry, Feinberg School of Medicine Northwestern University, 303 E. Superior St., Chicago, IL 60611, United States

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Events Calendar 2011

January 19-20,
BioBusiness
London, United Kingdom

January 27-28
Predictive Human Toxicity and ADME/Tox Studies 2011
Brussels, Belgium

January 29-February 2
LabAutomation 2011
Palm Springs, United States

February 1-2
2011 Pharma Market Research Conference
Parsippany, United States

February 6-8
5th Drug Discovery for Neurodegeneration
San Diego, United States

February 7-10
3rd International Conference and Exhibition on Drug Discovery and Therapy
Dubai, United Arab Emirates

February 13-16
Natural Products Conference 2011
Sharm el Sheikh, Egypt

February 14-17
Therapeutic Approaches to Neurodegeneration - Age Modifiers, Proteostasis, and Stem Cells
Nassau, Bahamas

February 16-19
Electrochemistry Conference 2011
Sharm el Sheikh, Egypt

February 21-23
World Antibody Drug Conjugate Summit Frankfurt, Germany

February 22-24
2011 International Conference on Bioinformatics and Computational Biology III ROUND
Haikou, China

February 22-25
Medicinal Chemistry Conference 2011
Sharm el Sheikh, Egypt

February 23-25
International Conference on Bioscience, Biotechnology, and Biochemistry
Penang, Malaysia

February 26-28
2011 International Conference on Bioscience, Biochemistry and Bioinformatics
Sentaosa, Singapore

March 4
Discussion Workshop: Perfecting the ELISPOT - a time for answers
London, United Kingdom

March 4-11
Inorganic Reaction Mechanisms
Gordon Research Conferences
Galveston, United States

March 7-8
Fragments 2011 - Third RSC-BMCS Fragment-based Drug Discovery meeting
Stevenage, United Kingdom

March 9-13
10th International Conference on Alzheimers and Parkinsons Diseases
Barcelona, Spain

March 13-18
Pittcon 2011
Atlanta, United States

March 17-20
EMBO|EMBL Symposia: Seeing is Believing - Imaging the Processes of Life
Heidelberg, Germany

March 20-22
The molecular biology of inflammatory bowel diseases
Durham, United Kingdom

March 21-23
World Congress on Biotechnology
Hyderabad, India

March 23-25
BIT's 4th Annual Protein and Peptide Conference
Beijing, China

March 25-27
2011 3rd International Conference on Bioinformatics and Biomedical Technology 3rd round call for paper
Sanya, China

March 27-April 2
EMBO Practical Course - Methods in Chemical Biology
Heidelberg, Germany

April 6-8
Faraday Discussion 150: Frontiers in Spectroscopy
Basel, United States

April 6-8
Membrane Proteins: Structure and Function
Oxford, United Kingdom

April 11-12
7th SCI-RSC symposium on Proteinase Inhibitor Design
Basel, United States

April 11-14
First EuCheMS Inorganic Chemistry Conference (EICC-1)
Manchester, United Kingdom

April 18-19
Analysis of free radicals, radical modifications and redox signalling
Birmingham, United Kingdom

April 20-21
BioFine Europe Exhibition 2011
Cambridge, United Kingdom

May 1-6
46th EUCHEM Conference on Stereochemistry
Brunnen, United States

June 1-5
EMBO Conference Series - Chromatin and Epigenetics
Heidelberg, Germany

June 15-17
Spectroscopy - Detective in Science
Rostock, Germany

June 15-18
3rd International Symposium on Metallomics
Münster, Germany

July 11-13
Ubiquitin Conference
Philadelphia, United States

July 17-22
Charge Transfer in Biosystems - ESF-LFUI Conference
Obergurgl, United States

July 18-20
2nd International Congress on Analytical Proteomics
Ourense, United States

August 3-4
From beads on a string to the pearls of regulation: the structure and dynamics of chromatin
Cambridge, United Kingdom

August 7-12
15th International Conference on Biological Inorganic Chemistry (ICBIC 15)
Vancouver, United States

August 28-September 2
Microscopy Conference 2011
Kiel, Germany

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INSTRUCTIONS TO AUTHORS

GENERAL INFORMATION

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The columns in the issues of *WJBC* will include: (1) Editorial: To introduce and comment on major advances and developments in the field; (2) Frontier: To review representative achievements, comment on the state of current research, and propose directions for future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Basic Research: To provide guidelines for basic research; (6) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (7) Review: To review systemically progress and unresolved problems in the field, comment on the state of current research, and make suggestions for future work; (8) Original Articles: To report innovative and original findings in biochemistry and molecular biology; (9) Brief Articles: To briefly report the novel and innovative findings in biochemistry and molecular biology; (10) Case Report: To report a rare or typical case; (11) Letters to the Editor: To discuss and make reply to the contributions published in *WJBC*, or to introduce and comment on a controversial issue of general interest; (12) Book Reviews: To introduce and comment on quality monographs of biochemistry and molecular biology; and (13) Guidelines: To introduce Consensuses and Guidelines reached by international and national academic authorities worldwide on the research in biochemistry and molecular biology.

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There are unstructured abstracts (no more than 256 words) and structured abstracts (no more than 480). The specific requirements for structured abstracts are as follows:

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Key words

Please list 5-10 key words, selected mainly from *Index Medicus*, which reflect the content of the study.

Text

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Figures should be numbered as 1, 2, 3, *etc.*, and mentioned clearly in the main text. Provide a brief title for each figure on a separate page. Detailed legends should not be provided under the figures. This part should be added into the text where the figures are applicable. Figures should be either Photoshop or Illustrator files (in tiff, eps, jpeg formats) at high-resolution. Examples can be found at: http://www.wjgnet.com/1007-9327/13/4520.pdf; http://www.wjgnet.com/1007-9327/13/4554.pdf; http://www.wjgnet.com/1007-9327/13/4891.pdf; http://www.wjgnet.com/1007-9327/13/4986.pdf; http://www.wjgnet.com/1007-9327/13/4498.pdf. Keeping all elements compiled is necessary in line-art image. Scale bars should be used rather than magnification factors, with the length of the bar defined in the legend rather than on the bar itself. File names should identify the figure and panel. Avoid layering type directly over shaded or textured areas. Please use uniform legends for the same subjects. For example: Figure 1 Pathological changes in atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: …*etc.* It is our principle to publish high resolution-figures for the printed and E-versions.

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Acknowledgments

Brief acknowledgments of persons who have made genuine contributions to the manuscript and who endorse the data and conclusions should be included. Authors are responsible for obtaining written permission to use any copyrighted text and/or illustrations.

REFERENCES

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Format

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Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua Zazhi* 1999; **7**: 285-287

In press

3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

Units

Use SI units. For example: body mass, m (B) = 78 kg; blood pressure, p (B) = 16.2/12.3 kPa; incubation time, t (incubation) = 96 h, blood glucose concentration, c (glucose) 6.4 ± 2.1 mmol/L; blood CEA mass concentration, p (CEA) = 8.6 24.5 μg/L; CO_2 volume fraction, 50 mL/L CO_2, not 5% CO_2; likewise for 40 g/L formaldehyde, not 10% formalin; and mass fraction, 8 ng/g, *etc.* Arabic numerals such as 23, 243, 641 should be read 23 243 641.

The format for how to accurately write common units and quantums can be found at: http://www.wjgnet.com/1949-8454/g_info_20100309232449.htm.

Abbreviations

Standard abbreviations should be defined in the abstract and on first mention in the text. In general, terms should not be abbreviated unless they are used repeatedly and the abbreviation is helpful to the reader. Permissible abbreviations are listed in Units, Symbols and Abbreviations: A Guide for Biological and Medical Editors and Authors (Ed. Baron DN, 1988) published by The Royal Society of Medicine, London. Certain commonly used abbreviations, such as DNA, RNA, HIV, LD50, PCR, HBV, ECG, WBC, RBC, CT, ESR, CSF, IgG, ELISA, PBS, ATP, EDTA, mAb, can be used directly without further explanation.

Italics
Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
Genotypes: *gyrA*, *arg* 1, *c myc*, *c fos*, *etc.*
Restriction enzymes: *Eco*RI, *Hin*dI, *Bam*HI, *Kbo* I, *Kpn* I, *etc.*
Biology: *H. pylori*, *E coli*, *etc.*

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Ocean International Center,
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